Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1.

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Funding Grants: Lentiviral Gene Therapy for Infants with X-linked Severe Combined Immunodeficiency using Autologous Bone Marrow Stem Cells and Busulfan Conditioning

Public Summary:
BACKGROUND: Allogeneic hematopoietic stem-cell transplantation for X-linked severe combined immunodeficiency (SCID-X1) often fails to reconstitute immunity associated with T cells, B cells, and natural killer (NK) cells when matched sibling donors are unavailable unless high-dose chemotherapy is given. In previous studies, autologous gene therapy with γ-retroviral vectors failed to reconstitute B-cell and NK-cell immunity and was complicated by vector-related leukemia. METHODS: We performed a dual-center, phase 1-2 safety and efficacy study of a lentiviral vector to transfer IL2RG complementary DNA to bone marrow stem cells after low-exposure, targeted busulfan conditioning in eight infants with newly diagnosed SCID-X1. RESULTS: Eight infants with SCID-X1 were followed for a median of 16.4 months. Bone marrow harvest, busulfan conditioning, and cell infusion had no unexpected side effects. In seven infants, the numbers of CD3+, CD4+, and naive CD4+ T cells and NK cells normalized by 3 to 4 months after infusion and were accompanied by vector marking in T cells, B cells, NK cells, myeloid cells, and bone marrow progenitors. The eighth infant had an insufficient T-cell count initially, but T cells developed in this infant after a boost of gene-corrected cells without busulfan conditioning. Previous infections cleared in all infants, and all continued to grow normally. IgM levels normalized in seven of the eight infants, of whom four discontinued intravenous immune globulin supplementation; three of these four infants had a response to vaccines. Vector insertion-site analysis was performed in seven infants and showed polyclonal patterns without clonal dominance in all seven. CONCLUSIONS: Lentiviral vector gene therapy combined with low-exposure, targeted busulfan conditioning in infants with newly diagnosed SCID-X1 had low-grade acute toxic effects and resulted in multilineage engraftment of transduced cells, reconstitution of functional T cells and B cells, and normalization of NK-cell counts during a median follow-up of 16 months. (Funded by the American Lebanese Syrian Associated Charities and others; LVXSCID-ND ClinicalTrials.gov number, NCT01512888.).

Scientific Abstract:
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